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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/806,645	07/12/2001	Yuri Kolesnikov	62072(51590)	3048

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EDWARDS ANGELL PALMER & DODGE LLP
P.O. BOX 55874
BOSTON, MA 02205

EXAMINER	
WANG, SHENGJUN	
ART UNIT	**PAPER NUMBER**
1617	

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07/27/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/806,645	KOLESNIKOV ET AL.	
	Examiner	Art Unit	
	Shengjun Wang	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 May 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,7-9,14,15,19-22 and 27-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,7-9,14,15,19-22 and 27-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Double Patenting Rejections

1. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

2. Claims 1, 7-9, 14,15, 19-22, 27-29 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 2, 11-15 of U.S. Patent No. 6,825,203. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of '203 are directed to a topical composition in the form of lotion, cream gel, comprising morphine, lidocaine, and NMDA receptors, ketamine in particular. The ranges of the amounts of the active ingredients in the composition is overlaps with the ranges herein. Not the optimization of results affecting parameters is within the purview of an ordinary skill in the art.

3. Claims 1, 9, 14, 15, 19-22 and 27 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 27-35 of copending

Application No. 10/823365. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of '365 are directed to a topical composition in the form of lotion, cream gel, comprising morphine, and NMDA receptors, ketamine in particular. The ranges of the amounts of the active ingredients in the composition are overlaps with the ranges herein. Not the optimization of results affecting parameters is within the purview of an ordinary skill in the art.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 1, 9, 14, 15, 19-22 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Elkhoury et al. (US 5,589,480), in view of Yaksh (USPN 5849761), Mayer et al. (USPN 5840731), Gevirtz et al. (US 5,635,204) and Lin et al.

6. Elkhoury et al. teach a topical composition of opioid analgesic drug, particularly, morphine. The composition provides analgesic effect in a localized area and without a migration of the opioid drug into the blood stream. See, the abstract. The composition may be in the form of aqueous solution, spray, gel, cream, etc. See, particularly, the claims. The composition is

prepared so that morphine is applied in the amount of 2-3 mg per 6 square inch area. Concentration of morphine in the examples is about 1% by weight. (10 mg per ml). See, column 5, lines 1-25.

7. Elkhoury et al. do not teach expressly a combination of morphine and ketamine, or the further incorporation of other therapeutical agents.

8. However, Yaksh teaches methods and compositions for the treatment of peripheral hyperalgesia (Abstract). Topical compositions comprising opiates are taught for local administration without eliciting CNS side effects (i.e. those caused by activation of the central receptors) (Abstract). Peripheral use of opiates, such as morphine, is taught as known in the art (col. 3, line 58-col. 4, line 9). The disadvantage of the use of morphine in the topical compositions disclosed by Yaksh is that it is taught to have short duration of activity and to have systemic and CNS side effects when used at *high levels* (col. 3, line 58-col. 4, line 9). formulated in creams, gels, ointments, emulsions, solutions, elixirs, lotions, suspensions, tinctures, pastes, foams, aerosols, irrigations, sprays, suppositories, Effective concentrations of hyperalgesic compounds are bandages, etc. (col. 41, lines 7-12). Alkyl esters of fatty acids, propylene glycol and lecithin are disclosed as excipients for lotions (col. 42, lines 47-50; col. 43, line 50; col. 44, line 1). Aqueous solutions are taught (col. 44, lines 51-63).

9. Mayer et al. teaches that the analgesic effectiveness of a combination drug composition comprising at least one analgesic is significantly enhanced by the addition of an NMDA receptor antagonist (Abstract). Mayer et al. teaches compositions comprising a first analgesic, a second component, and an analgesia-enhancing amount of an NMDA receptor antagonist and methods of treatment for alleviating pain by the administration thereof (col. 1, lines 6-27; col. 2, lines 30-

col. 3, line 5; col. 4, line 67-col. 5, line 13). Analgesics are taught to be selected from fentanyl, morphine, etc. (col. 3, lines 57-65). NMDA receptor antagonists are taught to be selected from ketamine, etc. (col. 4, lines 33-50). Excipients such as condensation products of ethylene oxide are also taught (col. 5, line 14-col. 6, line 11). Administration is taught to be achieved orally, rectally, intravenously, intramuscularly, subcutaneously, intrathecally, epidurally, or intracerebroventricularly (col. 4, line 66-col. 5, line 3). It is also noted that the composition of Example 1 comprises about 4% of an opioid analgesic (codeine phosphate).

10. Gevirtz et al. (US 5,635,204) teaches that ketamine is also suitable for topical application. See, particularly, claim 8. Lin et al. teaches that it is well known in the art that NMDA receptor antagonists can abolish nociceptor hypersensitivity. Lin particularly teaches a combination of ketamine, a NMDA antagonist, morphine and bupivacaine. See, particularly, page 175 and 176.

11. Therefore, it would have been obvious to one of ordinary skill in the art, at the time the claimed invention was made, to formulate a topical composition, as instantly claimed, comprising morphine and ketamine, and optionally other agents, such as bupivacaine, for only peripheral use because (1) morphine is known to be used topically without affecting CNS as taught by Elkhoury et al; and Yaksh further teaches that the formulation of morphine for only peripheral use is known in the art when the concentrations are sufficiently low; and (2) Mayer et at. and Lin et al. teach that the addition of an NMDA receptor antagonist (e.g. ketamine) to an analgesic composition is known in the art to significantly enhance the analgesia and/or reduce the side effects of the analgesics provided thereby; (3) ketamine is also known to be suitable for topical application; and (4) combinational use of morphine, ketamine and other analgesics are known. One would have been motivated to prepare and utilize such a composition because of an

expectation of success in providing a topical composition suitable for peripheral relief with significantly enhanced analgesic effects, as taught by Mayer et al. and Lin et al., at a concentration low enough to avoid the systemic and CNS side effects of morphine taught by Yaksh.

12. Furthermore it would have been obvious to one of ordinary skill in the art at the time of the invention to arrive at a composition comprising the claimed amount of morphine because Yaksh teaches that it is known in the art that the concentration of morphine must be sufficiently low to avoid systemic and CNS side effects. It would have been obvious to the skilled artisan to optimize the concentration of morphine in the composition in order to avoid systemic or central delivery because "where the general conditions of a claim are disclosed in the prior ad, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). The limitation "effectively," does not particularly limit the claims other than an optimization of result affecting parameters.

13. Claims 7, 8, 28 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Elkhoury et al. (US 5,589,480), in view of Yaksh (USPN 5849761), Mayer et al. (USPN 5840731), Gevirtz et al. (US 5,635,204) and Lin et al. as applied to claims 1, 9, 14, 15, 19-23, 26 and 27 above, and further in view of Mackles et al. (USPN 5322683).

The references apply as disclosed above. The references lack the teaching of a local anesthetic.

Mackles et al. teaches that lidocaine is a topical analgesic (col. 3, lines 16-18).

It would have been obvious to one' of ordinary skill in the art at the time of the invention to add the lidocaine of Mackles et al. to the composition of the combined reference because (1)

the combined references teach a topical analgesic composition; (2) Mayer et al. teaches the use of a second analgesic', and (3) Mackles et al. teaches that lidocaine is a topical analgesic. One of ordinary skill in the art would have been motivated by an expectation of success in providing a second analgesic in further alleviating pain, as taught by Mayer et al.

Response to the Arguments

Applicants remarks submitted May 14, 2007 have been fully considered, but are not persuasive.

14. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

15. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Particularly, the cited references as a whole have taught or suggested all the limitations in the claims. Particularly, (1) morphine is known to be used topically without affecting CNS as taught by Elkhoury et al; and Yaksh further teaches that the formulation of morphine for only peripheral use is known in the art when the concentrations are sufficiently low; and (2) Mayer et at. and Lin et al. teach that the addition of

an NMDA receptor antagonist (e.g. ketamine) to an analgesic composition is known in the art to significantly enhance the analgesia and/or reduce the side effects of the analgesics provided thereby; (3) ketamine is also known to be suitable for topical application; and (4) combinational use of morphine, ketamine and other analgesics are known. One would have been motivated to prepare and utilize such a composition because of an expectation of success in providing a topical composition suitable for peripheral relief with significantly enhanced analgesic effects, as taught by Mayer et al. and Lin et al., at a concentration low enough to avoid the systemic and CNS side effects of morphine taught by Yaksh.

16. In response to applicant's argument that the examiner has combined an excessive number of references, reliance on a large number of references in a rejection does not, without more, weigh against the obviousness of the claimed invention. See *In re Gorman*, 933 F.2d 982, 18 USPQ2d 1885 (Fed. Cir. 1991).

Applicants contend that Yaksh teach away from the use of morphine (in topical composition). The arguments are not persuasive. It is well understood that side effect of a therapeutical agent would not necessarily prevent it from clinical use. As disclosed by Yaksh, morphine has been used topically in the art. The known side effect would motivate artisan to modify morphine containing topical composition.

17. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shengjun Wang whose telephone number is (571) 272-0632. The examiner can normally be reached on Monday to Friday from 7:00 am to 3:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SHENGJUN WANG
PRIMARY EXAMINER

Shengjun Wang
Primary Examiner
Art Unit 1617